

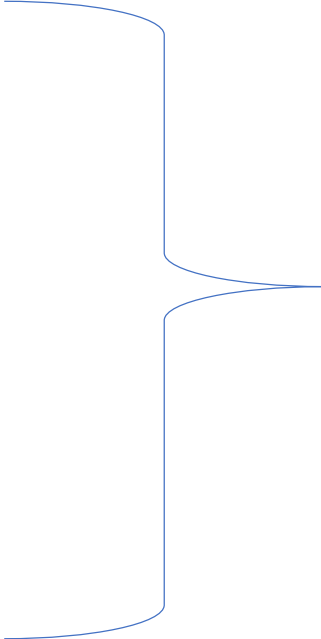
# Global Grand Rounds in ID

Presented by : Dr. Dhaval Dave  
Dr. D.Y. Patil Hospital, Pune, India

# History of presenting illness

- Patient is a 70 year old female, known diabetic, presented with chief complaints of :

- Right Hemicranial Headache
- Right Periorbital Pain and swelling
- Drooping of Right Eyelid
- Loss of Vision in Right Eye



6 days

# History of presenting illness

- Rt Hemicranial Headache since 6days
  - Acute onset
  - Throbbing type
  - Continuous
  - More in Right Frontal Area
  - Not associated with  
Photophobia/Phonophobia/Nausea/Vomiting/LOC
  - No prior history of headaches

# History of presenting illness

- Rt Periorbital Swelling & Pain
  - Noticed next day
  - Acute onset Periorbital & retroorbital throbbing continuous pain
  - Swelling & mild redness of periorbital area
  - Mild protrusion of Rt eye

# History of presenting illness

- Drooping of Rt Eyelid & Loss of Vision in Rt Eye
  - Noticed next day
  - Acute onset
  - Initially dropping of Rt Eyelid, Diplopia & Blurring of Vision
  - Few hours later complete loss of vision in Rt eye
  - No congestion, redness of Rt eye

# Past History

- Recovered from COVID-19 -- 14 days back
- Moderate disease
- Required Hospitalization, Oxygen support & Steroids (12days)
  
- Type 2 Diabetes Mellitus since 10 years
  - On OHA's – Metformin: 1000mg, Glimipiride: 2mg

# Exam

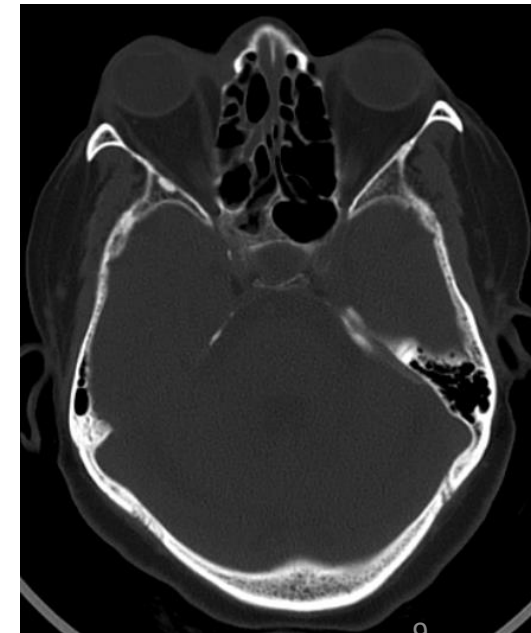
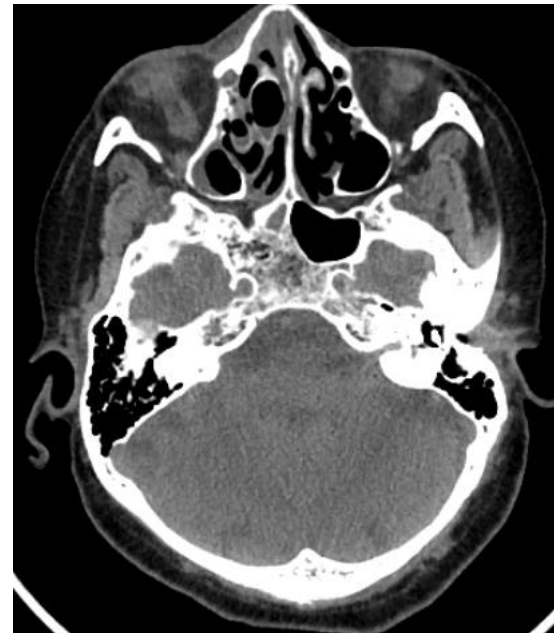
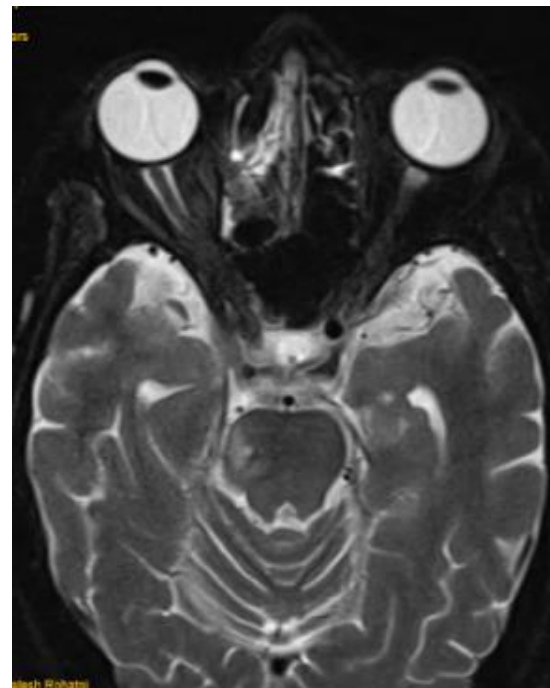
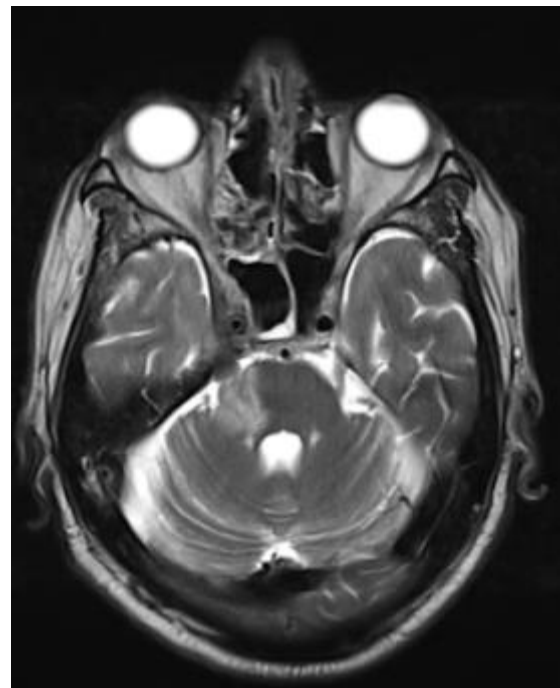
- Vitals: Normal
- Examination :
  - GCS: 15/15
  - No meningeal signs
  - Rt Frontal, Maxillary Sinus Tenderness present
  - Right Eye
    - Ptosis, Proptosis
    - No PL
    - Sluggish reaction to light, RAPD
    - All EOM restricted
    - Fundus: Normal
  - Left Eye
    - Normal
  - HMF / Motor / Sensory / Cerebellar Examination : Normal

# Labs

- Routine Lab Investigations : Normal
- Hba1c : 8.4
- RBS: 310mg/dl
- No Ketoacidosis



# Imaging

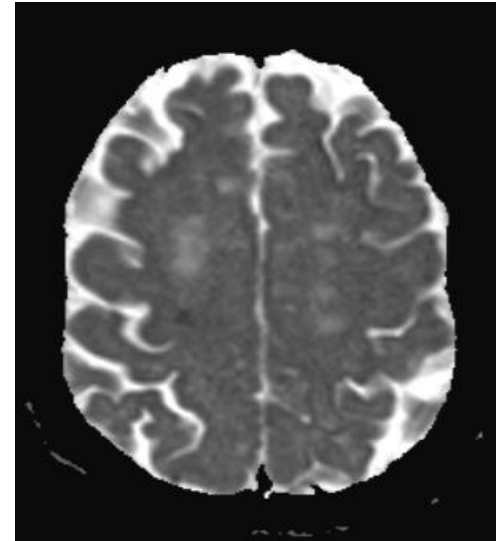
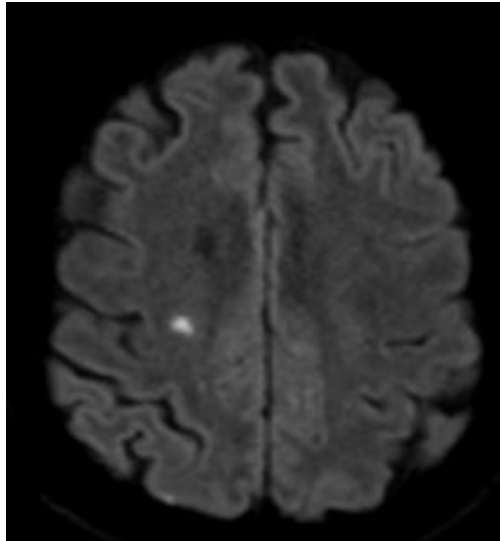


# Microbiology and course

- Nasal Swab for KOH : Fungal Hyphae seen – Suggestive of Mucor
- DNE showed : Black Necrotic Tissue – Suggestive of Mucor
- Liposomal Amphotericin B was started & continued (5mg/kg)
- Next day FESS – Surgical Debridement with Right Exenteration was done

# Clinical course

- On Postop Day 6 :
  - Fever with Encephalopathy & Left hemiparesis

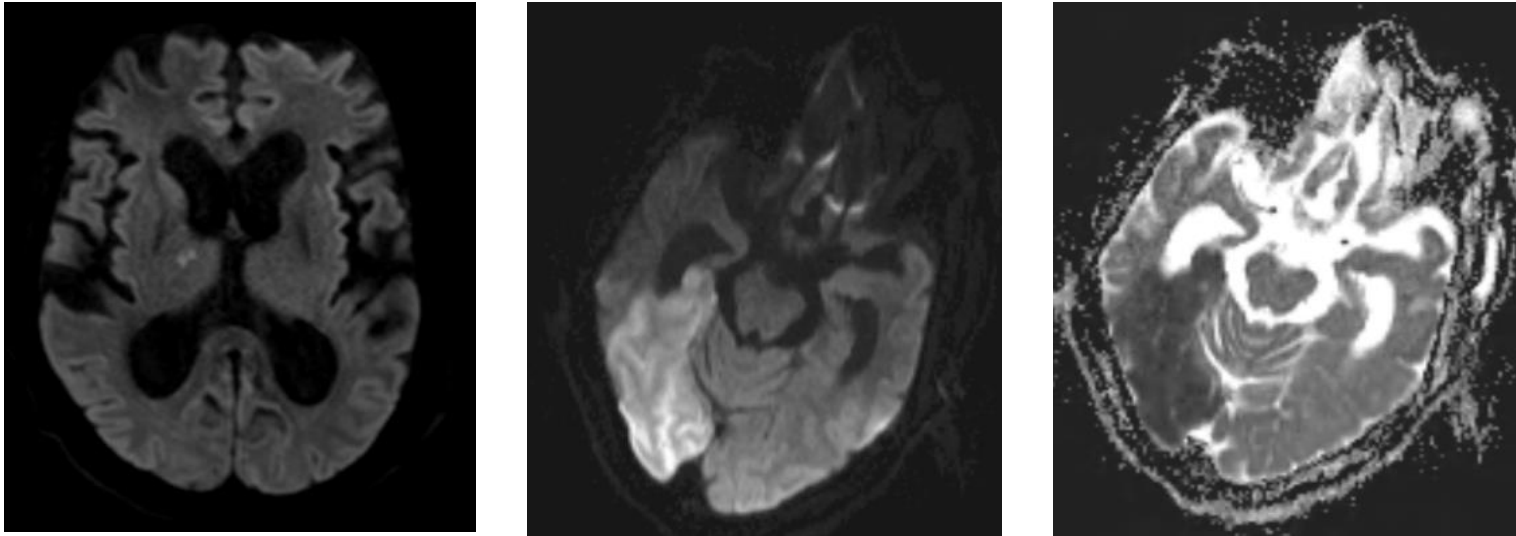


# Clinical course

- CSF Analysis :
  - Cells – 240/mm<sup>3</sup> (predominantly lymphocytic)
  - Protein – 112mg/dl
  - Sugar – 29mg/dl (Corresponding Bsl : 142mg/dl)
  - KOH, Gram Stain & Culture : Negative
- Procalcitonin : 0.32
  - Diagnosis:
    - **Fungal Meningitis (in view of very low sugar) with Rt Parietal Ischemic Stroke (Arteritis)**
    - **Possibility of Bacterial Meningitis cannot be completely ruled out**
- Dose of Liposomal Amphotericin B increased to 10mg/kg
- Started on Meropenem, Vancomycin, Anti-Platelet agents with anticoagulation

# Clinical course

- Patient showed improvement in sensorium with gradual recovery in Left Hemiparesis
- On Post-OP day 18 : Vomiting, Vertigo, Ataxia & Diminution of vision in Left Eye
- Repeat CSF Analysis :
  - Cells – 315/mm<sup>3</sup> (predominantly lymphocytic)
  - Protein – 114mg/dl
  - Sugar – 12mg/dl (Corresponding Bsl : 128mg/dl)
  - KOH, Gram Stain & Culture : Negative
- Procalcitonin : 0.23



In addition to Liposomal Amphotericin B started Tab  
Posaconazole

# Clinical course

- After 3 days : Fever with Encephalopathy
- Urine Culture : Pseudomonas sp
- Procalcitonin : 3.9
- Started on Colistin & Ceftriaxone + Disodium Edetate + Sulbactam in addition to Liposomal Amphotericin B & Tab Posaconazole
- Final Diagnosis :
  - **Rhino-Orbital-Cerebral Mucormycosis with Fungal or Bacterial Meningitis with Urosepsis with Recurrent Ischemic Stroke**
- No improvement so far
- At present on Mechanical Ventilator with Inotropic Support

# Invasive Fungal Infection & Covid

- More than 8000 cases of Covid-19 associated Mucormycosis has been reported in India till date
- Pune District has reported 591 cases so far



# Mucormycosis in India

- Possible reasons why such high numbers from India :
  - India has second highest load of COVID cases
  - India is second highest in terms of diabetics
  - 47% of Indians are unaware of their diabetic status and only a quarter of all patients achieved adequate glycemic control on treatment
  - India has highest burden of Mucor in the world (140 cases per million)

# Pathophysiology: Hypothesis

- Immune dysregulation in COVID
  - Predisposes to secondary infections
- Hyperglycemic state in COVID
  - COVID induces damage of pancreatic islets resulting in new onset diabetes
  - There is a high expression of ACE-2 receptors in pancreatic islets
- Use of Immunosuppressive Drugs
  - Steroids
  - Tocilizumab

# Pathophysiology: hypothesis

- Alteration of Iron Metabolism occurs in severe COVID
  - Severe COVID-19 is a hyper-ferritinemic syndrome
  - High Ferritin Levels → Excess Intracellular iron → Generates Reactive Oxygen Species → Tissue damage
  - Release of free iron into circulation → Excess free iron in academic states is unique risk factor for mucor
- Mucor thrives on Zinc, so excessive of zinc supplements is also now hypothesized as one of the risk factor
- Endothelialitis observed in severe COVID
  - Endothelial adhesion & penetration are critical early steps in mucor
- Use of antibiotics
- Unknown

# Neurological Manifestations

- Cavernous Sinus Involvement / Orbital Apex Involvement
- Optic Neuritis
- Meningitis
- Skull base osteomyelitis
- Stroke (Direct arterial invasion / Arteritis)
- Intracranial Fungal granuloma
- Isolated Cerebral Mucormycosis

*Chikley, Ben-Ami, Kontoyiannis. Mucormycosis of the Central Nervous System. Journal of Fungi 2019; 5: 59 Available from: <http://dx.doi.org/10.3390/jof5030059>*

# Treatment

- Early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment
- Resection or debridement should be repeated as required
- Antifungal Treatment :
  - Amphotericin B
  - Posaconazole
  - Isavuconazole
- There are no definitive data to guide the use of antifungal combination therapy
- In case of extensive disease, rapid progression, or poor general condition, the addition of isavuconazole or posaconazole can be considered
- Treatment to be continued till complete clinical & radiological resolution

# What is New ?

- Available Data suggest :
  - More aggressive
  - Prolonged treatment is needed
  - Co-infections : Mucor & Aspergillus
- Newer technique : Calcofluor staining for faster diagnosis
- Treatment:
  - Antifungal combination therapy
  - Orbital Amphotericin
  - Irrigation of Sinuses with Amphotericin

# Unanswered Questions

- What are the additional risk factors?
  - Does steroid dose matter ? Any specific steroid ?
  - Severity of COVID, hospital stay ?
  - O<sub>2</sub>, ventilation, tubings ?
- Is it different from 'routine' mucor ?
- Is some different treatment needed ?
- What are poor prognostic indicators?
- Can we prevent it ?

Thank You !!